Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-3, 5-12 and 19-21 are pending in the application, with claim 1 being the sole independent claim. Claims 1 and 21 have been amended herein. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112

Claims 1-3, 5-12 and 19-21 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner has asserted that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Office Action, page 2, lines 12-16. Applicants respectfully traverse the rejection.

Claim 1 as amended in the Response filed October 19, 2006, specifies that the buffer solution is an acetate buffer solution containing less than 0.2% acetate or a citrate buffer solution containing less than 0.1% citrate. However, the Examiner has suggested that present application only provides support for sodium acetate trihydrate at levels below 0.2% - not acetate levels less than 0.1%. Similarly, the Examiner has suggested

that the application only provides support for citrate buffers at levels less than 0.1% - not buffers containing less than 0.1% citrate.

In response, claim 1 has been amended herein to specify that the buffer solution is an acetate buffer solution containing 0.044 to 15 mM acetate or a citrate buffer solution containing 3.87 mM or less citrate.

Support for a buffer solution containing 0.044 mM to 15 mM acetate can be found on page 13, under Example 2, lines 24 – 27, which refers to the use of 0.00006 – 0.2% sodium acetate trihydrate. The 0.2% sodium acetate trihydrate can also be identified as being 15 mM* sodium acetate trihydrate, which, based on stoichiometry, contains 15 mM acetate. Similarly, 0.00006% sodium acetate trihydrate corresponds to 0.044 mM. Furthermore, the buffer used in the Examples 1 – 5 and 7 included 4.8 mM acetate. A worker skilled in the art would recognize that the buffering agent in the sodium acetate trihydrate salt is acetate. It is the buffering agent and not the sodium counter ion or complexed water that affects the buffering capacity of the buffer solution. See also claim 4 as-filed which refers to an acetate buffer. Accordingly, the present application provides support for any acetate-containing buffer solution having the recited acetate concentration and, in our view, the claims should not be limited to a particular acetate salt.

Support for a buffer solution contain 3.87 mM or less citrate can be found, for example, on page 14, lines 7 – 8 and page 13, lines 26 – 27. On page 13, lines 26 – 27,

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* 0.2% = 0.2 g/100ml
= 2 g/L MW of sodium acetate trihydrate = 136.08 g/mol
∴ M = 2 g/L ÷ 136.08 g/mol
= 0.015 M
= 15 mM

reference is made to inhalation products that contain citrate buffer at a level that did not exceed 0.1%. The citrate buffer in this case is sodium citrate dihydrate (the United States' Food and Drug Administration Inactive Ingredient Guide (IIG) references only sodium citrate in relation to inhalation products, and sodium citrate is known to be a dihydrate in the solid state). The 0.1 % concentration of sodium citrate can also be identified as 3.4 mM†. As detailed above with respect to acetate, a worker skilled in the art would recognize that the buffering component of sodium citrate is the citrate. The sodium counter ion and the two complexed water molecules do not contribute to the buffering capacity. See also original as-filed claim 4 which refers to a citrate buffer. Accordingly, the present application provides support for any citrate-containing buffer solution having the recited citrate concentration and, in our view, the claims should not be limited to a particular citrate salt.

Therefore, as the rejection to claims 1-3, 5-12 and 19-21 has been rendered moot, Applicants respectfully request that the rejection of these claims under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. § 103

The Examiner has rejected of claims 1 – 3, 5 – 12 and 19 – 21 under 35 U.S.C. § 103(a) as being unpatentable over Asmus *et al.* in view of Watson *et al.* and further in view of the Practical Engineering reference and ScienceLab.com A, Material Safety Data

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† 0.1% = 0.1 g/100ml
= 1 g/L MW of sodium citrate dihydrate = 294.10 g/mol
∴ M = 1 g/L ÷ 294.10 g/mol
= 0.0034 M

Sheet: Sodium Acetate Anhydrous MSDS and ScienceLab.com B, Material Safety Data Sheet: Sodium Acetate Trihydrate MSDS. Applicants respectfully traverse this rejection.

Asmus teaches that solutions of methacholine buffered at a pH of approximately 8.3 are stable when stored frozen. These solutions were found to be unstable at room temperature.

Watson disclosed that methacholine chloride solutions undergo hydrolysis if the pH exceeds 6. In support of this statement, Watson tested methacholine solutions having a pH of 4, 5 and 6. There is no distinction made in Watson as to any improved stability observed in solutions having a pH in the range of 4 to 5.

In the previous response, it was pointed out that the methacholine chloride solutions disclosed in Watson cannot be considered to be "inhalable," since the acetate and citrate concentrations were too high. In contrast the amount of acetate or citrate included in the presently claimed formulation is acceptable for inhalation.

In reply to these arguments, the Examiner has stated his view that one of ordinary skill in the art would be motivated to decrease the amounts of the acetate or citrate levels in the old composition to make a composition comprising acceptable levels of pharmaceutically acceptable buffering agents as provided by government regulatory agencies.

However, Watson teaches away from the use of less buffer. Watson teaches that methacholine in basic solutions will undergo base-induced hydrolysis and that methacholine in saline (i.e., in the absence of a buffer) becomes acidic. This is undesirable since the unbuffered solution may be bronchconstrictive by virtue of pH

= 3.4 mM

alone. This phenomenon is shown in Figure 2 of Watson to become more pronounced as the concentrations of methacholine increases. Watson also observed a drop in pH when methacholine was added to the buffer solutions even though they contained relatively high concentrations of buffering agent (see, page 589, column 1, lines 32 – 35).

One of skill in the art having regard to Watson, would not have had any reason to lower the amount of buffering agent as less buffering capacity and lower stability would have been expected. Moreover, one of ordinary skill in the art would not have any reason to expect that a buffer solution having a lower buffering capacity (due to lower concentration of buffering agent) would be successful in stabilizing the methacholine solutions as demonstrated by the pH and potency stability of the formulations of the present invention (See, for example, Tables 9 – 26), even under accelerated storage conditions. These unexpected results serve to overcome any basis for *prima facie* obviousness that the Examiner may assert.

Asmus supports the finding of Watson that a buffer is preferred for storage of methacholine solutions, but makes use of a buffer solution including 0.275 % sodium bicarbonate and 0.4% phenol. Thus, Asmus does not provide the skilled worker with any reason to use of acetate or citrate buffers at the presently recited concentrations.

Furthermore, the claims of the present application are limited to formulations containing an acetate or citrate buffer solution having a pH of between 4 and 5. Neither Asmus nor Watson teach or suggest that this is the appropriate pH range for stable methacholine formulations.

The data provided in Example 1 of the present application, and in particular, the accelerated stability data (40°C) shown in Tables 5 – 8, clearly demonstrates that the

buffer solutions having pH in the narrow range of from 4 to 5 provides superior stability in comparison to the buffer solution at pH 6. In contrast, Watson discloses compositions comprising methacholine in various buffer solutions, including acetate and citrate buffers. However, the data in Watson merely suggests that the buffer solution should have a pH of at least 6. Asmus discloses formulations of methacholine in a buffered saline solution containing phenol and having pH of approximately 8.3 (see, page 1635, column 1, line 3). Thus, nowhere in Watson or Asmus is it taught or suggested that the pH of the buffer solution in the stable methacholine formulations should be between 4 and 5.

In making the rejection, the Examiner has also relied upon two MSDS documents to establish that sodium acetate anhydrous and sodium acetate trihydrate are respiratory irritants and that, therefore, one would use low levels of acetate in a methacholine composition.

Applicants respectfully disagree with the Examiner's analysis. As the Examiner will appreciate, the claimed formulation is a *solution*. As a necessary result, the solution will not contain sodium acetate anhydrous or sodium acetate trihydrate. Instead, the solution will contain fully solubilized sodium acetate. Thus, the supposed motivation to use low levels of acetate buffer are based upon an erroneous application of the prior art.

Applicants respectfully request that the rejections of the claims under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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